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EXAMINER	
MOORE, WILLIAM W	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,298	UEMURA ET AL.	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-57 and 59-85* is/are pending in the application.

4a) Of the above claim(s) *60-75,78-81,84 and 85* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-57,59,76,77,82 and 83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 10/01, 01/03, and 06/03
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Amendments

Applicant's cancellation of claims 1-54 and 58 and amendments of claims 57 and 76-78 in the communication filed August 20, 2003, are acknowledged. Claims 55-57 and 59-85 are now pending in the application and claims 60-75, 78-81, 84 and 85 are withdrawn from consideration pursuant to Applicant's election, discussed below.

Claim Objections

Claims 56 and 77 are objected to because of the following informalities: Claim 56 fails to properly refer back to claim 77 where it recites, at line 2, "according to 77", rather than "according to claim 77", as Applicant could have intended. Two consecutive clauses numbered "xii", appear in claim 77, rather than consecutive clauses numbered "xi and "xii" as Applicant may have intended. Appropriate correction is required. It is noted that the structure of, and terminology in, claims presented and examined herein differs substantially from the claim format commonly used in this national forum and that some terms used in the present claims may be artifacts of translation that fail to convey the meaning intended when the priority document was drafted. Revision of the claim is suggested and amendment of the claim terminology may benefit from a certified English translation of Applicant's November 18, 1998-filed priority document, required to overcome a rejection based on the prior art hereinbelow.

Election/Restrictions

Applicant's election **with** traverse of Group 1, claims 76, 77, 55-57, 59, 82 and 83, wherein the polypeptide elected has the 317-amino acid sequence of SEQ ID NO:2, or proprotease or mature protease fragments thereof, or variants or modified derivatives thereof, in the communication filed August 20, 2003, is acknowledged. At pages 26-27

of this communication Applicant both traverses the requirement for restriction among Groups 1-3 and 10 and requests that Groups 2, 3 and 10 be rejoined with Group 1 on the grounds that the four Groups comprise amino acid sequences that are "similar". Applicant fails to argue, however, that the four principal polypeptides share the same special technical feature or that the polypeptide of Group 1 lacks a special technical feature. An argument that the principal polypeptides share a special technical feature would be unavailing where elected and traversed subject matters of the claims include "variants" of any and all of the four principal polypeptides. Applicant also suggests that polypeptides of Groups 1, 2, and 3 have "a common serine protease activity" but there is no disclosure in the specification that the proteases of SEQ IDs NOs:2, 4, 6 or 20 of these Groups recognize and cleave the same substrate and unrelated serine proteases, such as trypsin, chymotrypsin, and subtilisin, will also have a generic "serine protease activity" in common with the elected protease of Group 1 where the specification fails to define any particular "serine protease activity". Indeed, Example 4(2) at pages 72 and 73 of the specification identifies no specific substrate that the protease of SEQ ID NO:2 recognizes and cleaves among the ten that Applicant designates for assay which might allow a determination that a protease of SEQ IDs NOs:4, 6, or 20 may share a particular proteolytic activity with the protease of SEQ ID NO:2. The requirement for restriction between Group 1 and Groups 2-44 - a requirement that divides clauses (a), (b), (q)-(t) from clauses (c)-(p) and (u)-(gg) of claim 76 as currently amended and further divides clauses (i)-(iii) and (xxv)-(xxx) from clauses (iv)-(xxiv) and (xxxi)-(lvii) of claims 77 and 57 as currently amended - is still deemed proper and is therefore made FINAL.

Claims 77, 55-57, 59, 82 and 83 are examined to the extent that they describe those polynucleotides, vectors, and host cells that comprise the nucleic acid sequences indicated in clauses (i)-(iii) and (xxv)-(xxx) of the currently amended claim 77, as well as

recombinant methods of making the encoded polypeptide utilizing such polynucleotides, and the currently amended claim 76 is examined to the extent it describes polypeptides having amino acid sequences defined by its clauses (a), (b), and (q)-(t).

Claim Rejections - 35 USC § 101

35 U.S.C. § 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 55-57, 59, 76, 77, 82 and 83 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility.

A claimed invention must posses a specific, substantial and credible *in vitro* or *in vivo* utility, but the instant application cannot identify any specific, substantial, utility for the protease having the amino acid sequence set forth in SEQ ID NO:2 known to the inventors at the time the application was filed. It is agreed that the protease having the 317-amino acid sequence of SEQ ID NO:2 is identical in sequence with prior art human serine proteases disclosed by Darrow et al. and Ashkenazi et al., discussed below, yet claims 76, 82 and 83 lack utility because the instant specification discloses no specific *in vitro* utility, nor any kind of *in vivo* activity, for the polypeptide having the 317-amino acid sequence of SEQ ID NO:2, for proprotease or mature protease fragments thereof, or for variants or modified derivatives thereof. Claims 55-57, 59, 76 and 77 lack utility because the instant specification discloses no any specific *in vitro* utility, nor any kind of *in vivo* activity, for isolated nucleic acid sequences encoding the polypeptide having the 317-amino acid sequence of SEQ ID NO:2, including the nucleic acid sequence set forth in SEQ ID NO:1, and because the instant specification discloses no any specific utility for vectors that comprise a nucleic acid sequence of claim 77, and host cells comprising the vectors can express no protease having a specific utility where Applicant identifies no substrate recognized and cleaved by an encoded protease, *in vivo* or *in*

vitro, and identifies no specific cellular or extracellular function of the encoded protease. A method of use of a material for further research to determine, e.g., a specific biological role, in order to identify or confirm a "real world" context for its use, cannot be considered to be a "substantial utility". *Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966).* Mere allegations of a prospective, potential, utility cannot rise to the level of a credible assertion of a specific *in vivo* utility that is substantial. This is particularly the case for a pharmaceutical compound of claim 83 where the specification can identify no medical condition or disease that involves any function of the protease having the 317-amino acid sequence of SEQ ID NO:2. Indeed, the diffuse assertions of the specification indicate the contrary, that Applicant knew no specific utility at the time the application was filed for a protease having the 317-amino acid sequence of SEQ ID NO:2, or for a nucleic acid sequence encoding the protease, that would permit the immediate use by the public of this disclosed protease, a nucleic acid sequence that encodes it, or the use of a vector or cell comprising such a nucleic acid sequence.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 55-57, 59, 76, 77, 82 and 83 are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 55-57, 59, 76, 77, 82 and 83 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection addresses the subject matters of clauses (b), (r) and (t) of claim 76 and subject matters of claims 82 and 83 to the extent they relate to clauses (b), (r) and (t) of claim 76 and addresses as well the subject matters of clauses (iii), (xxvii) and (xxx) of claim 77 and subject matters of claims 55-57 and 59 to the extent they relate to clauses (iii), (xxvii) and (xxx) of claim 77. The specification fails to exemplify or describe the preparation of the subject matters of the divergent proteases of clauses (b), (r) and (t) of claim 76, clauses that reach generic proteins that differ to an undefined extent – "several amino acids" – in alteration of the positions in the amino acid sequence of SEQ ID NO:2 yet neither the claims nor the specification describe where any alterations might occur nor what the differences should be and the specification does not otherwise disclose or suggest the nature or source of any of the generic proteins that meet the limitations of the claims. In the case of hybridizing polynucleotides of clauses (iii), (xxvii) and (xxx) of claim 77, the specification fails to exemplify or describe the preparation of the subject matters of nucleic acid sequences encoding divergent proteases that differ at as many as 90% of the positions[1] in the amino acid sequence of SEQ ID NO:2, yet neither the claims nor the specification describe where any alterations might occur, nor what the differences might be, and the specification does not otherwise disclose or suggest the nature or source of any of divergent nucleic acid sequences, other than the non-elected species, that meet limitations of the claims. "While one does not need to have carried out one's invention before filing a patent application, one does need to be

[1] Where generic "stringent" hybridization conditions permit a nucleotide sequence divergence of about 30% by comparison to a reference sequence, such as SEQ ID NO:1 herein, nothing in the claims or specification requires that such divergence be limited to particular codon positions. Thus, non-identity at 30% of the nucleotide sequence positions can result in a 90% non-identity of the amino acid positions in an encoded polypeptide where first codon positions are the non-identical positions because when 30% of the 951 nucleotides - 285 - of SEQ ID NO:1 encoding the 317 amino acids of SEQ ID NO:2 alter first codon positions, an encoded amino acid sequence of the same length may have 285/317, i.e., 90%, amino acid sequence alterations.

able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification furnishes no relevant identifying characteristics of a protease that diverges at as many as "several" 14 amino acid positions from the sequence of SEQ ID NO:2 nor does it provide any characteristic, such as particular proteolytic activity, that permits correlation between undisclosed structures of any of the generic proteins of claim 76 or the encoding, hybridizing, polynucleotides of claim 77.

In addressing the issue of whether a disclosure of a molecular structure of one polypeptide of one biological species could adequately describe the molecular structure of a functionally similar molecule of another biological species, the Court of Appeals for the Federal Circuit held that a claimed invention must be described with such "relevant identifying characteristic[s]" that the public could know that the inventor possessed the invention at the time an application for patent was filed, rather than by a mere "result that one might achieve if one had made that invention". *University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Indeed, the claims rejected herein are, like the claims invalidated by the appellate panel in *University of California v. Eli Lilly*, designed to embrace polynucleotides encoding other, unknown, human polypeptides. Thus the specification's treatment of the claimed subject matter is entirely prospective where skilled artisans in the relevant field of molecular biology could not predict the structure, or other properties, of generic proteases clauses (b), (r) and (t) of claim 76 or hybridizing polynucleotides of clauses (iii), (xxvii) and (xxx) of claim 77.

Claims 55-57, 59, 76, 77, 82 and 83 are rejected under 35 U.S.C. §112, first paragraph, because the specification is not enabling for any embodiment of human protease having an amino acid sequence that diverges from the amino acid sequence of SEQ ID NO:2 by amino acid substitutions, deletions and insertions, or combinations thereof at as few as "several" or as many as 285 of the amino acid positions of SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, make and use the invention commensurate in scope with these claims.

Claims 76 and 77 contemplate arbitrary assignments of any or all of amino acid substitutions, additions or deletions in a protease, or a nucleic acid sequence encoding a protease, at as few as "several" amino acid positions in its primary structure, according to claim 76, or at as many as about 285 positions according to claim 77.[2] This rejection is stated under the first paragraph of the statute because the specification cannot support introduction of even "several", or as many as 285, amino acid alterations in the amino acid sequence of SEQ ID NO:2 where amino acid insertions, deletions, or substitutions occur anywhere, in any combination or any pattern, in the preproprotease, proprotease, and mature protease amino acid sequence set forth in SEQ ID NO:2. Indeed, while the prior art made of record herewith discloses an alteration in the amino acid sequence of SEQ ID NO:2, it is the substitution of alternative signal peptide and proprotease regions for the native signal peptide and proprotease regions and changes only the amino-terminus of the protease domain of SEQ ID NO:2 identified in the instant specification, thus cannot alter its native proteolytic activity. Because the specification fails to disclose the nature of a particular proteolytic activity of the protease having the amino acid sequence set forth in SEQ ID NO:2, it can provide no guidance as to the nature of amino acid sequence alterations within the protease domain that would assure that it retains any useful activity.

It is well settled that 35 U.S.C. § 112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. § 112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed.

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[2] See footnote 1, above.

Cir. 1988) (recognizing and applying the "*Forman*" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement). The standard set by the CCPA, the precursor of the Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope asserted in the claimed subject matter and the scope of guidance the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (scope of enablement varies inversely with the degree of unpredictability of factors involved in physiological activity of small peptide hormone). The Federal Circuit approved the standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997).

The Federal Circuit also considered whether definitional statements might enable a claim scope extending beyond a native amino acid sequence of a disclosed polypeptide product to embrace another, variant, polypeptide encoded by an altered DNA sequence. *Genentech, Inc. v. The Wellcome Found. Ltd.*, 29 F.3d 1555, 31 USPQ2d 1161 (Fed. Cir. 1994). The court held that only a narrow structural and functional definition was enabling precisely because the sweeping definitions of scope in the patent specification could not reasonably have been relied upon by the PTO in issuing the patent. *Genentech,* 29 F.3d 15 at 1564-65, 31 USPQ2d at 1168. Applying the "*Forman*" factors discussed in *Wands*, ***supra***, to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate, specific, guidance for altering the amino acid sequence of the protease domain SEQ ID NO:2 to the extent recited in the claims,

b) the specification lacks working examples wherein the amino acid sequence of the protease domain of SEQ ID NO:2 is altered to the extent recited in the claims, and,

c) unpredictability exists in the art where no members of the class of human proteases represented by amino acid sequences of SEQ ID NO:2 have had as many as, e.g., 285 amino acids identified for concurrent modification.

Thus the scope of subject matters embraced by the phrases "several" and "hybridizable . . . under stringent conditions", is unsupported by the present specification even if taken in combination with teachings available in the prior art.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 55-57, 59, 76, 77, 82 and 83 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 76, and claims 82 and 83 depending therefrom, are indefinite because claim 76 recites, in each of clauses (b), (r) and (t), "and having the same property as that of the protein having the amino acid sequence . . . of SEQ ID NO:2" but fails to specify the nature of the property to be compared to determine what is "same" and what is not. Claim 76, and claims 82 and 83 depending therefrom, are further indefinite where claim 76 recites, in each of clauses (b), (r) and (t), "derived from the amino acid sequence . . . by deletion, substitution or addition of one to several amino acids" because use of the term "several" is ambiguous in permitting an unlimited number of alterations where the resulting, "derived", protein need have no structural relationship to the protein having the amino acid sequence . . . of SEQ ID NO:2.

Claim 77, and claims 55-57, 59, depending therefrom, are also indefinite because claim 77 recites, "having the same property as that of the protein having the amino acid sequence . . . of SEQ ID NO:2", but fails to specify the nature of the property to be compared among encoded polypeptides to determine what is "same" and what is not. Claim 77, and claims 55-57, 59, depending therefrom, are further indefinite where claim 77 recites, "hybridizable with a nucleotide sequence . . . under stringent conditions" because many stringent conditions for hybridization are known in the art and the public, seeking to determine the scope of the intended subject matter, cannot know how to

define the degree of structural identity of the hybridizing sequence to the reference sequence. This aspect of the rejection may be overcome by amending claim 77, or a successor claim, to state the hybridization conditions set forth at page 33, lines 13-18, of the specification.

Claim 56 is independently indefinite in reciting, "in an expressible state", because the nature of an "expressible state" is not defined in the specification and the public seeking to ascertain the scope of the claim cannot know whether the "state" is particular to any kind of cell, requires the actual process of transcription or permits only the potential for transcription, or whether multiple states may be maintained by a cell.

Claim 57 is independently indefinite in several ways due to its recitation, "process . . . which comprises . . . cells transformed with . . . according to (i) to (xv) . . . or (xlix) to (liv) of claim 77 or a fragment thereof, and collecting hBSSP4 produced". First, numeric indicators in the form of lower case Roman numerals have no relationship to nucleotide sequences; this ambiguity can be remedied by reciting "clauses" in the claim. Second, several clauses occur in claim 77 which fall within Applicant's reference that describe fragments of a disclosed nucleotide sequence, rendering the description "or a fragment thereof" in claim 57 ambiguous, thus indefinite, because the public, seeking to determine the scope of the claim, cannot know what a fragment of a fragment might be. Third, the acronym hBSSP4 is ambiguous where the specification fails to identify a particular protease as "hBSSP4" and the range of clauses Applicant uses to describe what might have been intended in the claim permits no recovery of a particular product.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in-

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 55-57, 59, 76, 77 and 83 are rejected under 35 U.S.C. § 102(e)(1) as being anticipated by Ashkenazi et al., Published U.S. Applications Nos. 2002/0132240, 2002/0146709, 2002/0160374, 2002/0192659, 2002/0197671, and 2002/0198366, each made of record herewith.

Six U.S. patent applications of Ashkenazi et al. published in 2002 commonly share the disclosure of the corresponding PCT publication WO 99/14328 of Wood et al., made of record with Applicant's Information Disclosure Statement filed October 2, 2001, of the amino acid sequence of the PRO343 protease and its encoding nucleic acid sequence. Only Publication No. 2002/0132240, the earliest, is discussed herein for the sake of brevity but each of the six published U.S. Patent Applications is based on International Application PCT/US98/19330 filed September 16, 1998, as a priority document. The six published U.S. Applications and WO 99/14328 disclose the nucleic acid sequence, see Figure 97, encoding the 317-amino acid sequence of the PRO343 protease and, see Figure 98, its encoded amino acid sequence wherein the signal peptide, propeptide and active-site histidine region of a serine protease are identified. While the publication of Wood et al., WO 99/14328, is unavailable as prior art under 35 U.S.C. § 102(a), the disclosure thereof became prior art under 35 U.S.C. § 102(e)(1) upon publication in at least the six cited U.S. Patent Applications of Ashkenazi et al.

Ashkenazi et al.('240) disclose the 317-amino acid sequence of the human PRO343 protease identical to the entire amino acid sequence of SEQ ID NO:2 herein, as well as its encoding nucleic acid sequence captured as a cDNA in paragraphs 0193-0195, 0402, 0403, 0408, 0413, 0567, 0744, 0745, 0914, 1343, 1346, 1348, 1349, 1464, 1617,

Figs. 97 and 98, and SEQ IDs NOs:262 and 263. Ashkenazi et al.('240) also disclose, paragraph 0451, vectors that comprise a nucleic acid sequence encoding the PRO343 protease, host cells transformed with vectors comprising protease-encoding nucleic acid sequences, and recombinant methods for producing the encoded PRO343 protease utilizing vectors comprising protease-encoding nucleic acid sequences and transformed animal [CHO] cells, *E. coli* cells, and other host cells comprising the vectors. Ashkenazi et al.('240) also disclose, paragraphs 0469 and 0470, preparation of pharmaceutical compositions comprising a PRO343 protease and a pharmaceutically acceptable carrier as well as preparation of medicaments comprising the PRO343 protease.

Claims 55-57, 59, 76, 77, 82 and 83 are rejected under 35 U.S.C. § 102(e)(2) as being anticipated by Darrow et al., US 6,426,199, made of record herewith.

Issuing on an application filed in the United States before the November 19, 1999, filing date of Applicant's International Application, Darrow et al. disclose the 317-amino acid sequence of the human protease C-E identical to the entire length of SEQ ID NO:2 herein and its encoding nucleic acid sequence. **See**, SEQ IDs NOs:1 and 7. Darrow et al. further disclose the amino acid sequence of a fusion polypeptide comprising the protease domain of the human protease C-E, and its encoding nucleic acid sequence, that is identical to SEQ ID NO:2 herein from position 8 to position 268 of the positive-numbered amino acid positions of SEQ ID NO:2 herein, differing therefrom at "several" amino acid positions of the protease domain's amino terminus. **See**, SEQ IDs NOs:2 and 8. Darrow et al. also disclose the preparation of vectors and transformed host cells comprising nucleic acid sequence encoding either the native or the variant C-E protease where the nucleic acid sequences encoding the proteases are maintained in a suitable context suitable for their expression, as well as recombinant methods of producing either the native or the variant C-E protease and recovering the expressed product utilizing these vectors and transformed host cells. **See**, columns 3-11 and 24-27.

Darrow et al. additionally disclose methods for identifying inhibitors of the protease C-E, and conditions and specific substrates for which the C-E protease has specific activities. **See**, columns 28 and 29 and Table 1. Darrow et al. further disclose the preparation of a pharmaceutical composition comprising the C-E protease for the treatment of specific medical conditions, skin-flaking or dandruff. **See**, column 24 at lines 9-27.

It is noted that the International Patent Application PCT/JP99/06472, supplied by Applicant and of record herein, filed after the application issuing as the U. S. Patent to Darrow et al. was published in Japanese and that the priority document, Japan Patent Application 10-347813, for this International Application, also supplied by Applicant and of record herein, filed before the application issuing as the U. S. Patent to Darrow et al. was also printed in Japanese. Thus Applicant may be able to overcome this rejection of claims herein by submitting certified English translations of both Japanese language documents and demonstrating the disclosure common to both that enable, and provide an adequate written description of, subject matter within the claims pending herein prior to the filing date of the application issuing as the U. S. Patent to Darrow et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claim 82 is rejected under 35 U.S.C. § 103(a) as being unpatentable over any of Ashkenazi et al., Published U.S. Applications 2002/0132240, 2002/0146709, 2002/0160374, 2002/0192659, 2002/0197671, and 2002/0198366, as applied to claim 76 above, in view of Egelrud et al., U.S. Patent No. 5,834,290, made of record herewith.

The teachings of Ashkenazi et al. discussed above are taken as before and the additional teaching of Ashkenazi et al.('240) is now cited of "method[s] of identifying agonists or antagonists to a PRO polypeptide which comprise[s] contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide [where p]referably[ ] the PRO polypeptide is a native PRO polypeptide", see paragraph 0468. Ashkenazi et al.('240) teach no specific method of screening for a serine protease inhibitor comprising comparing the enzymatic activity of the PRO343 protease in the presence and absence of contact with a candidate inhibitor compound, essentially an *in vitro* assay. Thus the teachings of Egelrud et al. are now cited of a method of screening for a serine protease inhibitor comprising comparing the enzymatic activity of a human serine protease in the presence and absence of contact with several candidate inhibitor compounds, see column 24, lines 5-22, and column 48 lines 26-53 and Table 5. It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the screening assays of Egelrud et al. in a method to identify an inhibitor of the PRO343 protease of Ashkenazi et al.('240) comprising comparing the enzymatic activity of the PRO343 protease in the presence and absence of contact with a candidate inhibitor compound because Ashkenazi et al.('240) teach that identifying an antagonist, i.e., an inhibitor, of any of their PRO polypeptides, including the PRO343 protease, is worthwhile and because Egelrud et al. teach and demonstrate the use of an assay comparing the enzymatic activity of a serine protease sharing significant homology with the protease of Ashkenazi et al.('240) in the presence and absence of contact with a candidate inhibitor compound to identify at least three inhibitors and determine their relative ability to inhibit serine protease activity.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is. 703.308.0583 until about January 21, 2004, and will be 571.272.0933 thereafter. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at 703.308.3804 until about January 21, 2004, and at 571.272.0928 thereafter. The fax phone numbers for all communications for the organization where this application or proceeding is assigned is 703.872.9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore
December 23, 2003

NASHAAT T. NASHED PHD.
PRIMARY EXAMINER